IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIOGEN INTERNATIONAL GMBH and BIOGEN MA INC.,	)	
Plaintiffs,	)	**C.A. No. 17-823-LPS (Consolidated)**
v.	)	
AMNEAL PHARMACEUTICALS LLC, et. al,	)	
Defendants.	)	

BIOGEN'S OPENING BRIEF ON SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS AND INJUNCTIVE RELIEF

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MS	Multiple sclerosis
DMT	Disease-modifying therapy
’514 patent	U.S. Patent No. 8,399,514
DMF	Dimethyl fumarate
QD	Once daily
BID	Twice daily
TID	Thrice daily
MRI	Magnetic resonance imaging
ARR	Annualized relapse rate
EMA	European Medicines Agency
ANDA	Abbreviated New Drug Application
PTO	United States Patent & Trademark Office
Gd+	Gadolinium-enhancing
ECTRIMS	European Committee For Treatment and Research in Multiple Sclerosis
FF	Biogen’s Opening Post-Trial Proposed Findings of Fact
PTX	Plaintiffs’ Trial Exhibit
DTX	Defendants’ Trial Exhibit
PDX	Plaintiffs’ Demonstrative

I. INTRODUCTION

Pursuant to the Stipulated Order entered January 8, 2020, this brief and its accompanying proposed findings address (1) secondary considerations of non-obviousness and (2) injunctive relief.

Defendants had the burden of proof at trial to establish invalidity by clear and convincing evidence. Meeting that high burden is even more difficult where, as here, Defendants' obviousness case relied on prior art already considered by the Patent Office. The burden of persuasion remained at all times on Defendants. Not only did they fail to meet this burden on the ultimate question of invalidity, but they also failed to even meet their initial burden of production of establishing a *prima facie* case of obviousness based on the asserted prior art. Biogen will address the latter in its answering brief and accompanying proposed findings due February 28, 2020. In the interim, this brief addresses the secondary considerations of non-obviousness that compel a holding of non-obviousness even if the Court were to conclude that Defendants had demonstrated a *prima facie case* of obviousness.

A court must consider secondary considerations of non-obviousness, also referred to as objective indicia of non-obviousness, as part of an obviousness analysis. Such secondary considerations include unexpected results, long-felt but unmet need, commercial success and copying. Here, Biogen presented compelling evidence at trial regarding (1) the claimed invention's surprising and unexpected results in Biogen's Phase III trials, (2) the long-felt but unmet need for an oral MS therapy, (3) the commercial success of Tecfidera®, a commercial embodiment of the claimed invention, and (4) copying of the claimed invention by more than twenty-five ANDA filers. This evidence establishes the non-obviousness of the claimed invention, in addition to the reasons to be addressed in Biogen's upcoming answering brief on validity.

As to unexpected results, Biogen established that the '514 patent's claimed method of treating MS with 480 mg/day of DMF is a novel and non-obvious medical advance that surprised not only the MS community when Biogen released the results of its Phase III clinical trials using this method, but also its own personnel and outside investigators involved in those trials. In fact, Biogen's own statisticians were so surprised by the Phase III results that they did not believe them at first and therefore re-ran the calculations to ensure they were correct. The Phase III efficacy results were not only dramatically superior to those in Phase II, but it was also particularly surprising that the magnitude of the efficacy for the not-previously-tested 480 mg/day dose was on par with that of the 720 mg/day dose, especially given the lackluster performance of the 720 mg/day dose in the Phase II trials. The unexpectedness of these results is supported by fact testimony, expert testimony and contemporaneous documents supporting such testimony. For example, Defendants' own expert acknowledged in his own contemporaneous writings that the results were "better than [he] would have expected." Defendants offered no evidence rebutting these unexpected results but for an erroneous "plateau" theory that Defendants' Dr. Stobbe presented as part of his obviousness assertions, which Biogen will address in its validity brief.

The impressive Phase III efficacy and safety results derived from Dr. O'Neill's invention claimed in the '514 patent satisfied a long-felt but unmet need for a first-line oral MS therapy. No oral MS therapy existed at the time of the 2007 filing date of the '514 patent. Instead, MS patients required either self-injection or intravenous administration, which had many drawbacks limiting long-term adherence and leading some patients to decline therapy entirely. This long-felt but unmet need even continued after two oral MS therapies were marketed after the filing date of the '514 patent due to the side-effect profiles and safety concerns associated with those products. In contrast, Tecfidera® satisfied that need when it came to market in 2013. As Dr. Duddy testified,

the introduction of Tecfidera® was "disruptive" to his practice due to so many patients demanding this new therapy.

The resounding and undisputed marketplace success of Tecfidera® further demonstrates the non-obviousness of the claimed invention. Tecfidera®'s success, resulting in billions of dollars of sales every year, has been driven by the efficacy, safety, tolerability and convenience benefits flowing from the use of the claimed method. The copying of Tecfidera® by over twenty-five ANDA filers also constitutes further evidence of the non-obviousness of the claimed invention.

II. SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS COMPEL A HOLDING THAT DEFENDANTS FAILED TO ESTABLISH INVALIDITY BY CLEAR AND CONVINCING EVIDENCE

A. Defendants Bear the Burden of Establishing Invalidity

The burden of proving invalidity by clear and convincing evidence rests at all times on a patent challenger. 35 U.S.C. § 282; *Microsoft v. i4i Ltd. P'ship*, 564 U.S. 91, 97 (2011); *Mas-Hamilton Grp. v. LaGard, Inc.*, 156 F.3d 1206, 1216 (Fed. Cir. 1998) ("the presumption of validity remains intact and the ultimate burden of proving invalidity remains with the challenger throughout the litigation."); *see also Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1534 (Fed. Cir. 1983) ("In the end, the question is whether all the evidence establishes that the validity challenger so carried his burden as to have persuaded the decisionmaker that the patent can no longer be accepted as valid.").

Moreover, "in determining what would have been obvious to one of ordinary skill in the art at the time of invention, the use of hindsight is not permitted." *In re Alfuzosin Hydrochloride Patent Litig.*, 2010 WL 1956287, at *3 (D. Del. May 14, 2010). "[O]bjective indicia of non-obviousness play an important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016); *see also Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Indeed, "[objective indicia] may

often be the most probative and cogent evidence of non-obviousness in the record." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009) (internal quotations and citations omitted); *see also Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1303 (Fed. Cir. 2010). A court therefore must consider such objective indicia, often also referred to as secondary considerations, as part of an obviousness analysis. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357-58 (Fed. Cir. 2013) ("[C]onsideration of the objective indicia is *part of* the whole obviousness analysis, not just an after-thought.") (emphasis in original). Secondary considerations include, *inter alia*, unexpected results, long-felt but unmet need, commercial success and copying. *See Graham*, 383 U.S. at 17-18; *Procter & Gamble Co.*, 566 F.3d at 997-98.

B. Unexpected Results

Objective evidence of non-obviousness includes the unexpected properties of the invention compared to the prior art. *Graham*, 383 U.S. at 17-18. Unexpected results need not be recognized as of the priority date to be relevant to non-obviousness. *See Knoll Pharm. Co. v. Teva Pharms. USA Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) ("There is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent application contains all the work done studying the invention, in order for that work to be introduced into evidence in response to a litigation attack."). A patent owner may demonstrate unexpected results by "show[ing] that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995) ("[W]hen an applicant demonstrates substantially improved results . . . and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary.") (emphasis in original). Biogen has proven the substantially improved results of the claimed method of treating MS with 480 mg

DMF, dosed twice daily. The claimed method in Biogen's Phase III trials demonstrated surprising efficacy unexpected by the entire MS community. Moreover, Defendants have not offered any evidence, either through Dr. Stobbe or on cross-examination of Dr. Duddy, calling into question the results seen in Biogen's Phase III trials. Accordingly, the unrebutted and unexpected Phase III results are compelling evidence of the non-obviousness of the claimed invention.

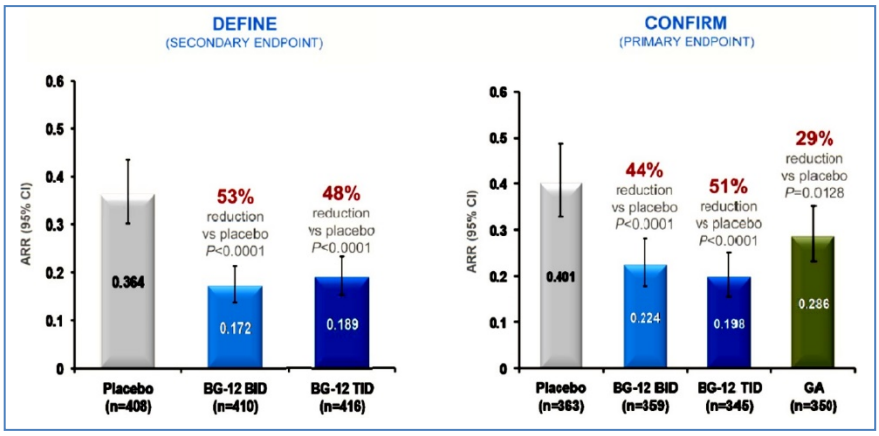
1. The Phase III Results Surprised the MS Community

a. 480 mg/day DMF Demonstrated Unexpected Efficacy

Given Biogen's Phase II study results, a skilled artisan would not have expected the results for 480 mg/day DMF seen in Biogen's Phase III trials. In 2004, Biogen initiated a randomized, double-blind, placebo-controlled Phase II clinical trial to evaluate three orally administered doses of DMF in MS patients: (a) 120 mg QD (120 mg/day); (b) 120 mg TID (360 mg/day); and (c) 240 mg TID (720 mg/day). (FF 12-13.) Only the highest 720 mg/day dose met the primary endpoint, statistically significantly reducing the mean number of new Gd+ lesions on brain MRI scans (weeks 12-24) compared to placebo. (*Id*. 17.) 720 mg/day also produced statistically significant results on several secondary endpoints and showed a trend toward reducing annualized relapse rate with a 32% reduction compared to placebo. (*Id.*) By contrast, 120 mg/day and 360 mg/day did not achieve statistical significance for any of the primary or secondary endpoints. (*Id.* 15-16.)

Following this Phase II trial, Biogen conducted two randomized, double-blind, placebo-controlled Phase III trials (DEFINE and CONFIRM) using a 720 mg/day dose and Dr. O'Neill's long-proposed 480 mg/day dose. (FF 18-25.) These trials unexpectedly demonstrated that the lower 480 mg/day dose (240 mg BID) had a similar magnitude of efficacy as the higher 720 mg/day dose (240 mg TID) on all primary and secondary endpoints. (*Id.* 20-21, 24-25.) Moreover, the efficacy of both doses was substantially greater than expected based on the Phase II study.

The unexpected and impressive results of Biogen's Phase III trials were detailed during prosecution of the '514 patent application. For example, Dr. Rudick illustrated the surprising efficacy of 480 mg/day DMF in statistically significantly reducing annualized relapse rate ("ARR") compared to placebo:



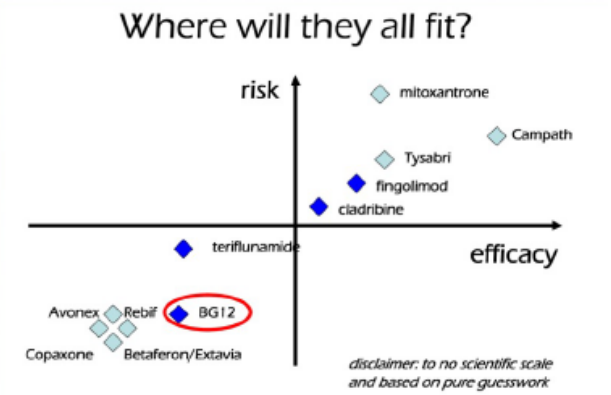
(FF 26-27.) The reduction in ARR seen in both Phase III trials also demonstrated that 480 mg/day had similar efficacy to 720 mg/day, with both doses unexpectedly "hovering on either side of 50 percent" in reducing the relapse rate. (*Id.*; Duddy 405:17-406:8.)

b. 480 mg/day Demonstrated an Unexpected Magnitude of Effect

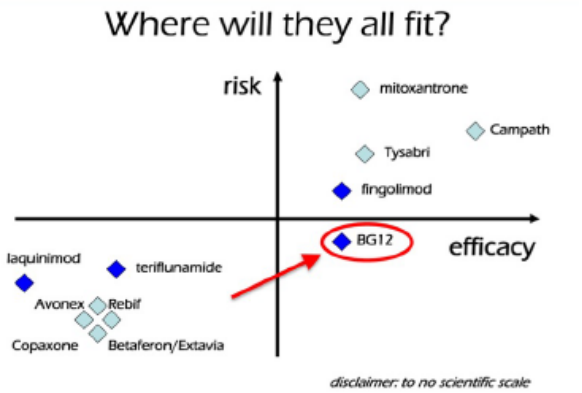
Skilled artisans would not have expected, and could not have predicted, the Phase III results based on the Phase II results. Biogen's Phase II study showed that only the highest 720 mg/day dose achieved statistically significant results, and those were modest at that. (FF 28-30, 40.) One skilled in the art therefore would not have expected that a lower 480 mg/day dose would be effective in treating MS, let alone be similarly efficacious as 720 mg/day. (Duddy 402:20-403:2 ("[A]bsolute surprise that we have a drug at a dose not tested, not only doing better than the new expectations that we had, but actually overtaking the higher dose, and then landing in very much the same efficacy range as that higher dose after the phase III.").)

The magnitude of the effects (clinical and radiological) in the Phase III trials surprised the MS community. In 2007, injectable interferon and glatiramer acetate therapies reduced relapse rate by 30%, which Dr. Lindsey characterized as "modestly effective." (FF 29; *see also* Duddy 389:6-7 ("So we have first line low efficacy injectable therapies.".) Similarly, 720 mg/day DMF demonstrated an "unimpressive, interferon like" reduction in relapse rate of roughly 30% in the Phase II studies. (FF 30; Duddy 487:8-11; *see also id.* 393:19-23 ("We can anticipate from this, from the clinical figure that we're looking at a drug that might be interferon like in the efficacy, from the radiology data that is perhaps the most you could hope for.".)

Dr. Duddy testified that skilled artisans would not have expected that a 480 mg/day dose would exceed the effects of the 720 mg/day dose in Phase II. And his testimony is supported by his contemporaneous analysis of the Phase II and Phase III results. For example, in a 2009 presentation before the Phase III results were known, Dr. Duddy anticipated that the 720 mg/day dose of DMF (BG12) from Phase II would be a lower efficacy drug:



(FF 31-32.) But in November of 2011 after Phase III results were announced, Dr. Duddy reworked the same slide he presented in 2009 and moved DMF (BG12) to the lower right quadrant as the sole MS drug having the strongest overall performance, balancing both safety and efficacy:



(*Id.* 33-34.) In view of the moderate efficacy of 720 mg/day DMF in Phase II, it was surprising that 480 mg/day not only provided strong efficacy but also efficacy that was similar in magnitude to that of the much higher 720 mg/day dose. *(Id.*)

Moreover, contemporaneous evidence generated by Defendants' expert Dr. Lindsey also establishes that skilled artisans would not have expected a 480 mg/day dose to exceed the effects of the 720 mg/day dose in Phase II. For example, before the Phase III trials concluded, Dr. Lindsey reported Biogen's Phase II results on his personal website, stating that DMF "reduced relapse rate by about 30% compared to placebo." (FF 35.) He added that "[t]he combination of increased effectiveness and safety is elusive." (PTX214; Lindsey 155:4-21.) Then, after the first of the two Phase III studies concluded, Dr. Lindsey expressed his surprise at the impressive and unexpected results obtained, noting that "[t]he most important results were from a Phase III study of a drug called BG12." (PTX215; PDX003-31; Lindsey 156:5-18; *see* FF 36-38.) He noted that the "annual relapse rate on placebo was 0.364, while it was 0.172 on the lower dose [480 mg/day] BG12 and 0.189 on the higher dose [720 mg/day] of BG12. This is a reduction of 53 or 48% in the relapse rate." (PTX215; *see also* Lindsey 156:19-22.) Dr. Lindsey also noted that, for the 480 mg/day dose, "[t]here was also a marked effect on MRI activity, with a reduction of about 90% in enhancing lesions and 85% in new T2 lesions." (PTX215.) Dr. Lindsey thus reported: "[t]hese

are ***impressive results, both for efficacy and safety***. In their Phase II study . . . this drug reduced relapse rate by 30%, so these results are a little ***surprising***." (*Id.*) (emphasis added).

Consistent with Dr. Duddy's testimony, Dr. Lindsey testified with respect to the first Phase III study that "there was a . . . considerably better effect in the phase III studies . . . . So [the Phase III results] were ***better than I would have expected***." (Lindsey 157:14-21; Duddy 411:20-412:17; *see also* Lindsey 156:23-158:5 (Q: Aside just from the posting, you believed that these results were a lot better in phase III than the phase II results would have led you to expect; is that right? A: Yes, I was expecting about a 30 percent reduction in relapse rate from phase III based on what we had found in phase II.") (emphasis added).) Furthermore, Dr. Lindsey's contemporaneous writings following the first Phase III study concluded that a "second phase III study is in progress, and the results should be available soon. If they see the same benefits, this will be an attractive medicine." (PTX215.) After those results came out, Dr. Lindsey praised the positive results (PTX216; PDX003-31) and reiterated that "[t]he results of the first Phase III study (see ECTRIMS 2011) were ***quite impressive***." (PTX216 (emphasis added); Lindsey 158:10-25; Duddy 414:13-14.) Dr. Lindsey's analysis and testimony further confirm that skilled artisans can and do compare clinical study results at different doses and across trials. (FF 39.)

The testimony and contemporaneous documents of Dr. Lindsey and Dr. Duddy demonstrate that skilled artisans would not have expected, and in fact did not expect, 480 mg/day to exceed the effects of 720 mg/day in Phase II. Their surprise at the impressive and unexpected Phase III results establishes the non-obviousness of the claimed invention. *See In re Soni*, 54 F.3d at 750 ("[T]hat which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. The principle applies most often to the less predictable fields . . . ."); *see also Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306 (Fed. Cir. 2015) ("[T]he prior art

taught that 200 ppm BAK would either have no impact on the permeability of bimatoprost or decrease it. [Patentee's] inventors surprisingly determined that the opposite was true, namely, that 200 ppm BAK enhanced the permeability of bimatoprost. That is an unexpected difference in kind that supports nonobviousness.").

In addition, radiological outcomes in Phase III also surprised skilled artisans. In Phase II, 720 mg/day DMF statistically significantly reduced new/newly enlarging T2 lesions, a secondary endpoint, by 48%. (FF 40.) Dr. Duddy testified that T2 lesion reduction "helps us form a view of the magnitude of the effect we're likely to see clinically," and contemporaneous with the Phase II results, other MS therapies demonstrated "T2 reduction rates of 80 percent. 50 percent is well short of what we have been seeing with therapies whose level of magnitude that we already know." (*Id.*; Duddy 393:6-14.) In the DEFINE Phase III study, 720 mg/day unexpectedly reduced T2 lesions by 74%, and 480 mg/day exceeded this effect with an 85% reduction. (FF 40.) One skilled in the art would not have predicted the magnitude of effect of 720 mg/day in a longer, bigger study, and most certainly would not have predicted that the lower dose of 480 mg/day would exceed that effect. (*Id.*) Accordingly, skilled artisans would not have expected the magnitude of efficacy of 480 mg/day seen in Phase III based on the Phase II results.

2. The Phase III Results Surprised Biogen Personnel and Investigators

The reactions of Biogen personnel and investigators involved in the development of Tecfidera® when they first analyzed and announced the Phase III results further evidences the surprising and unexpected nature of those results. (FF 41.) For example, Dr. Dawson led the Phase III studies and carried Tecfidera® through FDA approval (Dawson 284:15-23; 285:6-11), and she and others involved in the clinical trials had the same expectations as other skilled artisans as discussed above, namely, that 720 mg/day in the Phase III trials would reduce relapse rate by roughly 30%. (FF 41-42.) However, as Dr. Dawson testified, when Biogen statisticians unblinded

and calculated the clinical data for the Phase III studies, "they were so surprised with the results that actually ***they figured they did something wrong*** and they started over from the beginning and completely reanalyzed the study." ((FF 43; Dawson 333:9-17; *see also id.* 333:18-334:14) (emphasis added).) And Dr. Dawson expressed her similar surprise and amazement at the results. (FF 44; Dawson 333:9-334:14.) In addition, before Dr. Dawson disclosed the DEFINE Phase III results to the principal investigators (esteemed clinicians in the field), they predicted relapse rate reductions for 720 mg/day of from "high 20s" to "high 30s." (FF 43.) When informed of the results for 720 mg/day, "[t]hey were incredibly thrilled and excited. It was very unexpected." (*Id.*) Dr. Dawson also testified that, when they were similarly asked about the 480 mg/day dose, "the thinking was that it would be less efficacious than the 720 milligram dose, and when we told them that the actual effect . . . was 53 percent effect on relapses, they were again, very surprised." (*Id.*)

Dr. Dawson also detailed the unexpected results of the Phase III DEFINE study in a declaration she submitted during prosecution of the '514 patent. (FF 44.) The Patent Office did not dispute these results. (PTX417 at BiogenF00007600 ("The unexpected and advantageous results demonstrated for the claimed method relative to the other embodiments that are disclosed in the instant specification are not in dispute.").) Dr. Dawson explained in that declaration, consistent with her trial testimony, that one skilled in the art would not have had a reasonable expectation that 480 mg/day DMF would provide statistically significant and clinically meaningful effectiveness for treating MS. (FF 44.) The surprise at the unexpected Phase III results expressed by Dr. Dawson and other skilled artisans involved in the development of Tecfidera® thus confirms the non-obviousness of the claimed invention to skilled artisans. *See In re Soni,* 54 F.3d at 750.

3. The Phase III Results Amounted to A Difference in Kind

The difference in results seen in Biogen's Phase II and Phase III studies is not just a difference in degree; it is a difference in kind. Based on the Phase II results, skilled artisans

expected DMF at the highest tested dose of 720 mg/day to exhibit, at best, interferon-like efficacy. *See supra* Section II.B.1. And the skilled artisan, based on the Phase II results, would not have reasonably expected that a lower 480 mg/day dose would treat MS with meaningful efficacy, let alone on the same scale as the higher 720 m/day dose. *See supra* Section II.B.1.-2. The Phase III results, however, surprisingly showed not only that the 480 mg/day and 720 mg/day doses greatly exceeded efficacy expectations based on the Phase II 720 mg/day results, but also that the lower 480 mg/day dose demonstrated an unexpected magnitude of effect similar to the 720 mg/day dose in the Phase III trials, and even exceeded it in some respects. (*See* Duddy 488:4-23.) This is a difference in kind.

Indeed, the medical profession's response to these surprising and unexpected results further establishes that the difference in the results for Phase II compared to Phase III is a difference in kind. For example, as discussed, Dr. Duddy and Dr. Lindsey testified that Tecfidera® (i.e., 480 mg/day DMF) is a substantially more effective MS treatment than interferons, and the MS Trust (a group providing information to MS patients and educating MS health professionals) similarly classifies Tecfidera® as more effective than interferons, elevating it to a higher class of MS therapies distinct from the less effective interferons. (FF 47.) Such perceptions further demonstrate that skilled artisans believe that the surprising and unexpected results of using 480 mg/day DMF constitute a difference in kind compared to expectations based on the Phase II results. (*Id.* 45-47); *see Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1274 (Fed. Cir. 2018) (reversing obviousness ruling and finding increased bioavailability of the claimed invention a difference in kind, not degree); *see also Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306-07 (Fed. Cir. 2015) (finding the "results exhibited by the claimed formulation . . . constitute[d] an unexpected

difference in kind, *viz.*, the difference between an effective and safe drug and one with significant side effects that caused many patients to discontinue treatment.").

C. Additional Objective Indicia of Non-obviousness

1. Long-Felt But Unmet Need

There was a long-felt but unmet need for a safe and clinically effective oral MS treatment prior to the 2007 filing date of the application that led to the '514 patent, as none existed at that time. (FF 48); *see Procter & Gamble*, 566 F.3d at 998 ("[W]e look to the filing date of the challenged invention to assess the presence of a long-felt and unmet need."). The claimed 480 mg/day DMF method for treating MS, embodied in Tecfidera®, met this need.

About 2.5 million individuals worldwide had been diagnosed with MS as of 2007. (Wynn 606:10-11.) MS is a chronic autoimmune disease requiring lifelong therapy. (FF 49.) Injectable MS therapies were available at that time, but they required regular injections or monthly parenteral infusions and had significant limitations, often associated with injection anxiety or injection-related adverse effects, thus limiting long-term adherence to treatment and leading many patients to decline disease-modifying therapy entirely. (*Id.* 50-51.) A clear need for oral MS therapy thus existed as of 2007. *See Procter & Gamble*, 566 F.3d at 998.

Tecfidera® is a first-line MS treatment that satisfied this need. It brought significant convenience to patients and greatly enhanced compliance, balancing therapeutic efficacy with tolerability, thus improving long-term benefits compared to injectable MS therapies. (FF 55.) As Dr. Duddy explained, "Tecfidera was really very disruptive for our center." (Duddy 414:22-23.) Dr. Duddy expressed surprise not only at "the number of people who were injecting who switched" but at "the amount of unexpressed need" by his patients. (Duddy 416:9-16.) Moreover, consistent with the economic evidence of Tecfidera®'s success (*see infra* Section II.C.2.), Dr. Duddy explained how certain patients who had previously declined therapy altogether came onto therapy

with Tecfidera®, and others chose not to switch from injectables to oral MS treatments, Gilenya® or Aubagio®, discussed below, knowing that Tecfidera® would soon be approved. (Duddy 415:1-23; 419:6-420:15.)

Gilenya® and Aubagio® were approved for marketing after the '514 patent's 2007 priority date and prior to Tecfidera®'s 2013 launch. Their entry to the market therefore does not bear on the issue of the long-felt but unmet need that existed at the time of the filing for the '514 patent, but the fact that some patients chose not to switch from injectables to those products highlights that the long-felt but unmet need for an oral MS treatment remained even after their approval. Indeed, Gilenya® (fingolimod) was approved in 2010 but was associated with serious side effects including teratogenicity (a potentially serious problem for women 20-45 years old, the most common group treated for MS), high blood pressure and cardiotoxicity (thus requiring burdensome monitoring), and liver toxicity. (FF 52.) These safety concerns led the EMA, for example, to approve fingolimod as a second-line treatment. (*Id.*) Aubagio® (teriflunomide), available in 2012, was similarly associated with serious side effects including potential birth defects, liver toxicity and hair loss, and it required fortnightly blood tests (necessitating venipuncture). (*Id.* 53.) These oral treatments thus did not satisfy the long-felt need. (*Id.*); *see In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1082 (Fed. Cir. 2012) ("Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand.").

Defendants suggested at trial that a 720 mg/day DMF dose like that tested in Biogen's Phase II study somehow satisfied the long-felt need. But no 720 mg/day dose of DMF was ever approved, and thus could never have fulfilled the long-felt but unmet need for an oral MS therapy.

See Otsuka Pharm. Co. v. Sandoz, Inc., No. 07-01000, 2010 WL 11636594, at *21 (D.N.J. Dec. 15, 2010) (uncommercialized drug cannot satisfy long-felt need).

2. Commercial Success

"Commercial success is a key secondary consideration that must be considered in an obviousness inquiry." *Mitsubishi Chem. Corp. v. Barr. Labs., Inc.*, 718 F. Supp. 2d 382, 435 (S.D.N.Y. 2010) (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)). The resounding success of Tecfidera® demonstrates the non-obviousness of the claimed invention.

a. Tecfidera® Is A Marketplace Success

Tecfidera®'s marketplace success is not disputed. Since its launch in 2013, Tecfidera® has achieved blockbuster status on an annualized basis, with total U.S. sales of $15.9 billion. (FF 56.) The market for MS disease-modifying therapies (DMTs) falls "generally into three classes--oral therapies, self-injected therapies, and intravenous or infused therapies. Within those classes, there are quite a number of options available to the marketplace. And at the end of 2018, there were at least 15 different solutions across those three classes . . . . It's a very crowded field, in part because it's a very serious disease . . . ." (*Id.*) By any comparison, Tecfidera® "has performed very well." (*Id.*; Jarosz 728:7-8.) Indeed, Tecfidera® led all products in 2018 "on a revenue basis" and "comprised about 20 percent . . . . of the marketplace of these 15 or 18 different competitors . . . ." (FF 57.)

Moreover, Tecfidera® had nearly double the market share of Gilenya® and Aubagio® by 2018 despite its later marketplace introduction. (FF 58.) And Tecfidera® "became the country's number one prescribed oral therapy for relapsing forms of MS after six months." (*Id.*) Tecfidera thus has been and remains a tremendous marketplace success. (*Id.* 59); *Pfizer Inc. v. Teva Pharms. U.S.A., Inc.*, 882 F. Supp. 2d 643, 671-72 (D. Del. 2012) ("[P]rescriptions for Lyrica® generated . . . over $2.3 billion in net revenue since . . . introduced in the United States in 2005" despite

"shar[ing] the market with many competing products . . . ."); *Shire Orphan Therapies LLC v. Fresenius Kabi USA, LLC*, 2018 WL 268097, at *19 (D. Del. June 5, 2018) ("Firazyr® is a commercial success due to its safety, convenience, and efficacy, compared to other acute treatments, as evidenced by its sales, profitability, and share of the acute HAE market.").

Additional evidence of Tecfidera®'s marketplace success includes that Tecfidera® performed "well in excess of what was projected" by Biogen, contrary to industry norms for drug launches. (FF 60); *Shire Orphan*, 2018 WL 2684097, at *19 (finding Firazyr® a commercial success where sales exceeded "even Plaintiffs' own forecasts"). Tecfidera® also received praise and recognition shortly after launch and one year later. (FF 61.) In addition, Biogen's and ANDA filers' investments and business planning further evidences Tecfidera®'s success. (*Id.* 64.) Biogen has invested significant resources in developing Tecfidera®. (*Id.*) Similarly, Defendants have committed substantial resources pursuing market entry through regulatory approval and litigation. (*Id.* 65.) Indeed, one ANDA filer's failed attempt to file on the very first regulatory date prompted a lawsuit where it claimed to have lost "tens if not hundreds of millions of dollars in revenue it otherwise would have earned through the sale of its generic version of Tecfidera®." (*Id.* 66.)

Defendants' expert, Mr. Hofmann, does not dispute Tecfidera®'s success, sales figures or its blockbuster status. (FF 62.) Mr. Hofmann also had no reason to believe that Tecfidera®'s discounts and allowances differed from those for Gilenya® and Aubagio®. (*Id.* 63.)[1] Mr. Hofmann also agreed that by Q4 2018, Tecfidera® had more sales than any other product to treat MS in the US. (*Id.* 62.) "[T]he numbers tell a pretty positive story." (*Id.*; Hofmann 823:13.)

[1] In his other work, Mr. Hofmann has also relied on the same type of data, Symphony Health data, upon which Mr. Jarosz relies in part to support his opinions. (*Compare* Jarosz 743:16-745:3 *with* Hofmann 820:2-5.)

Rather than contesting the commercial success of Tecfidera®, Defendants argue that Biogen cannot rely on that commercial success as an objective indicium of non-obviousness because a Biogen patent application (No. 10/197,077) and two Biogen patents (Nos. 6,509,376 and 7,320,999) somehow disincentivized competitors from entering the market. Defendants, however, have not presented any evidence that any of these documents actually disincentivized any company from developing any product, let alone prevented any company from entering the market. Defendants' "blocking patent" theories are also baseless because: (1) unissued claims in a patent application cannot block others, *Return Mail, Inc. v. U.S. Postal Serv.*, 139 S. Ct. 1853, 1859 (2019) and, as Mr. Hofmann agreed, claims in a published application can change before issuance of a patent (Hofmann 810:9-12); (2) U.S. Patent No. 7,320,999 issued after the 2007 filing date of the '514 patent (DTX341 at 1; Hofmann 810:5-8) and thus similarly cannot constitute a blocking patent, *see Prima Tek II, L.L.C. v. A-Roo Co.*, 222 F.3d 1372, 1379 n. 2 (Fed. Cir. 2000) ("A 'blocking patent' is an earlier patent that must be licensed in order to practice a later patent."); (3) U.S. Patent No. 6,509,376 is limited to microtablet or micropellet formulations that could not have prevented others from developing DMF in other forms for treating MS (DTX340 at 5-6), and Mr. Hofmann provided no technical support to the contrary; and (4) Defendants' pursuit of their ANDAs demonstrates that they themselves did not view these items as blocking them from developing their ANDA products.

b. The Claimed Invention's Benefits Have Driven Tecfidera®'s Success

"Commercial success requires a nexus to the claimed invention." *Apple Inc. v. Samsung Elecs. Co., Ltd.*, 839 F.3d 1034, 1054 (Fed. Cir. 2016) (en banc). "Once the patentee demonstrates a prima facie nexus, the burden of coming forward with evidence in rebuttal shifts to the challenger." *Crocs, Inc v. Int'l Trade Comm'n*, 598 F.3d 1294, 1311 (Fed. Cir. 2010). Biogen has

demonstrated a *prima facie* nexus between Tecfidera®'s success and the benefits of the claimed invention, and Defendants have not rebutted this evidence.

Biogen's economic expert Mr. Jarosz testified that the clinical benefits of the claimed invention was a driver of Tecfidera®'s marketplace success, basing this conclusion on a discussion with Dr. Wynn, Dr. Wynn's expert reports and Dr. Duddy's trial testimony about the clinical benefits of treating MS with 480 mg/day of DMF. (FF 70-71.) Specifically, he concluded that "the invention allows for a unique combination of four elements—efficacy, tolerability, safety and convenience," and the 480 mg/day dosing of DMF "yielded unexpected efficacy with improved patient compliance." (Jarosz 748:11-18; *see also id.* 771:2-4; PDX006-12.) Mr. Hofmann did not dispute the importance of these attributes of the patented invention to Tecfidera®'s commercial success: "I think it is true that efficacy, safety, tolerability and convenience are important drivers of the sales of Tecfidera . . . ." (FF 72; Hofmann 802:13-15; *see also id.* 804:15-18 ("[S]afety, efficacy, tolerability, convenience are things that are important to the commercial performance of Tecfidera . . . .").

Mr. Jarosz's testimony, and Mr. Hofmann's agreement therewith, is supported by Biogen's marketing materials that highlight the patented invention's attributes relating to efficacy, safety, tolerability and convenience (FF 73), as well as website-accessed information intended for physicians and patients that further emphasizes the patented invention's attributes of efficacy, safety, tolerability and convenience. *(Id.*) Third-party perceptions also confirm the clinical importance of the patented invention's benefits. For example, New York Times, Investor's Business Daily and Boston Globe articles highlight the benefits of efficacy, safety and tolerability. (*Id.* 74); *Shire Orphan*, 2018 WL 2684097, at *19-20 ("Third-party analysts . . . praised the unique properties of Firazyr® . . . ."). Similarly, Northstar Metric Tracker, which follows the "behaviors

and preferences of neurologists," found that "no MS drug consistently was perceived by the neurologists to be better than Tecfidera in both efficacy and safety," specifically, "[t]here was no drug that was higher than Tecfidera on the combination of efficacy and safety." (FF 75.) In sum, Biogen's marketing materials and third-party perceptions confirm the "advantages of the claimed invention [] in the marketplace. There is thus a causal nexus between the patented invention and the success of Tecfidera." (*Id.* 76.)

The existence of "pricing and marketing and promotion" do not detract from the patented benefits as significant drivers of Tecfidera®'s commercial success. (FF 77.) For example, pricing for Tecfidera® and oral DMTs Gilenya® and Aubagio® "track[] one another fairly closely." (*Id.*) Accordingly, "pricing alone is not responsible" for Tecfidera®'s commercial success. (*Id.*) Rather, "Tecfidera has been a success in the marketplace and its success has in large part been due to the patented invention. As a result, the patent is a commercial success." (*Id.*); *Shire Orphan*, 2018 WL 268097, at *19 ("The court finds that Firazyr® is a commercial success due to its safety, convenience, and efficacy, compared to other acute treatments, as evidenced by its sales, profitability, and share of the acute HAE market.").

3. Copying

Copying can also provide evidence of non-obviousness. *Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 991 (Fed. Cir. 1988). Here, that over twenty-five ANDA filers are copying Tecfidera® as claimed in the '514 patent further supports that the asserted claims are not obvious. *See Biogen Int'l GmbH v. Amneal Pharmaceuticals LLC et al.*, 17-cv-823 (D.I. 22 at 1-7); *Biogen Int'l GmbH v. Mylan Pharmaceuticals Inc.*, 17-cv-116 (N.D. W. Va. June 30, 2017) (D.I. 1). These ANDA filers reviewed the method of treatment claimed in the '514 patent and formulated their proposed generic products as direct copies of Tecfidera®. (FF 78.) *See Forest Labs., Inc. v. Ivax Pharms., Inc.*, 438 F. Supp. 2d 479, 496 (D. Del. 2006) ("The success of Lexapro® and its benefits

compared with other SSRIs is also supported by the efforts of generic drug manufacturers, including Defendants, to copy the claimed invention.").

III. Biogen Is Entitled to Injunctive Relief

Defendants did not dispute Biogen's evidence in support of injunctive relief to prevent launching of a generic product. Mr. Jarosz provided unrebutted testimony about (1) the irreparable harm to Biogen upon market entry of generic equivalents to Tecfidera® for which there is no adequate legal remedy, (2) the balance of harms warranting entry of a permanent injunction and (3) furtherance of the public interest in enjoining Defendants from market entry. (FF 79.) Defendants have all stipulated to infringement of the asserted '514 patent claims. (*Id.* 2, 10.) Moreover, Defendants have not met their heavy burden of proving invalidity of the '514 patent claims. Accordingly, Biogen is entitled to a permanent injunction pursuant to 35 U.S.C. § 271(e)(4)(B). *See eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388 (2006)); *Bristol-Myers Squibb Co. v. Mylan Pharm. Inc.*, C.A. No. 09-651-LPS (D. Del. Nov. 5, 2013) (Oral Order at D.I. 242). Similarly, for the reasons explained herein and those Biogen will explain in its responsive post-trial brief, Biogen is also entitled to a judgment pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval for each Defendant to make, use, offer to sale, sell, market, distribute or import its generic equivalent to Tecfidera® be no earlier than the expiration of the '514 patent. *See In re Armodafinil Patent Litig. Inc.*, 939 F. Supp. 2d 456, 503 (D. Del. 2013); *Merck & Cie v. Watson Labs., Inc.*, C.A. No. 13-1272-RGA (D. Del. Sept. 14, 2015) (Final Judgment at D.I. 116).

IV. Conclusion

For the reasons stated above and those Biogen will address in its responsive post-trial validity submissions, Biogen respectfully requests that the Court enter final judgment holding Biogen's '514 patent valid and infringed and grant Biogen's requested relief.

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